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Opposition against EP-B-1 534 289
Patentee: Kyowa Hakko Kogyo Co., Ltd.
Opposition by: Harvey Vaughan John Adams; Wächtershäuser & Hartz
Our Ref.: K3048 OPP(EP)

München, December 21, 2009
BE/RWA

This is in response to the Notices of Opposition which were filed by Harvey Vaughan John Adams and Wächtershäuser & Hartz.

1. Requests

1.1 It is requested to maintain the patent EP-B-1 534 289 (hereinafter referred to as the patent-at-issue) on the basis of the main request filed herewith.

Claim 1 of the main request corresponds to a combination of granted claims 1, 3 and 6 (claims 1, 2 and 5 as filed). Claim 2 of the main request corresponds to a combination of granted claims 2, 3 and 6 (claims 1, 2, 5 and 8 as filed).

1.2 As an auxiliary measure oral proceedings are requested.

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2. Prior art

Because the opponents used the designations D1 and D2 for different prior art documents a modified numbering will be used in the following to unambiguously identify the documents. The designations D1 to D23 as proposed by Opponent I will be used. WO 03/063876 (referred to as D1 by Opponent II) will be referred to as D24 and US 2008/0176873 (referred to as D2 by Opponent II) will be referred to as D25.

D16 and D18 were published after the priority date of the patent-at-issue. The priority date of D25 is even after the priority date of the patent-at-issue. Therefore, these documents should not be allowed into the present opposition proceedings.

D24 has an earlier priority date than the patent-at-issue. It was filed and published in the interval between the instant priority and filing dates. Consequently for the subject matter of the patent-at-issue which can validly claim priority D24 is only prior art for the assessment of novelty (Art. 54(3) EPC).

Opponent I tried to enter copies from the corresponding US prosecution as D21 into the current EP proceedings. The USPTO has very different standards and approaches regarding novelty and inventive step compared to the EPO. In addition the claims pending in the US are different from those which are the basis of the present opposition proceedings. For these reasons the findings of the USPTO are irrelevant for the current opposition proceedings.

3. Priority claim

In point 5.1 of his Notice of Opposition Opponent II argued that claim 2 of the patent-at-issue does not have a valid priority claim because the priority application does not disclose that an adenosine A_{2A} receptor antagonist is useful for treating nocturnal myoclonus. This assessment is not correct.

In the third paragraph on page 10 of the priority application it is mentioned that adenosine A_{2A} receptor antagonists can be used for treating RLS or "related disorders". It is immediately evident from the introductory part, in particular page 8, third paragraph to page 9, third paragraph, of the priority application that nocturnal myoclonus (also referred

to as PLMS) is related to RLS. Example 2 of the priority application explains that (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methylxanthine (referred to as "KW-6002") can be used to treat PLMS. Because the priority application does disclose that an adenosine A_{2A} receptor antagonist and in particular the compound referred to in instant claim 1 is useful for treating nocturnal myoclonus, the priority claim of claim 2 is valid. Consequently, D1 is only prior art for the assessment of novelty.

4. Objections under Art. 83 EPC

Neither of the opponents contested that granted claim 6, on which the present independent claims are based, is enabled.

5. Novelty

Instant claims 1 and 2 include the subject matter of granted claim 6. Opponent I did not contest the novelty of this claim. Opponent II took the position that granted claim 6 in as far as it refers to the treatment of RLS is anticipated by D24 (cf. points 6.1 to 6.6 of the Notice of Opposition). The patentee can not agree with this position.

Claim 1 of the patent-at-issue relates to the use of (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methylxanthine (referred to in the following as "KW-6002") or a pharmaceutically acceptable salt thereof for treating restless legs syndrome, i.e. the use of an individualized compound for treating a specific disorder. In contrast thereto, D24 mentions an adenosine A_{2A} receptor antagonist and a generic formula covering possible xanthine compounds (I) is given as an example (cf. e.g. claim 6).

In the section which describes the invention of D24 it is mentioned that

> *"The invention also includes methods of treating movement disorders comprising administering an effective amount of at least one adenosine A_{2A} receptor antagonist to a patient in need thereof. Such treatment can be therapeutic such as to treat tremors, bradykinesias, gait, dystonias, or tardive dyskinesias or other extrapyramidal syndromes, or preventative such as to prevent or lessen the effects of drugs that cause movement disorders."*

(D24: page 45, lines 7 to 12). As can be seen from this citation, the section which describes the invention of D24 does not mention that the adenosine A_{2A} receptor antagonist can be used to treat restless leg syndrome (hereinafter referred to as "RLS"). RLS is only mentioned on page 7, lines 28 and 29 of D24. However, this passage does not relate to the invention of D24 but is rather a description of the prior art. Here it is mentioned that various diseases involving dystonias are known:

> *"Diseases involving dystonias include hereditary spastic paraplegia (HSP), a group of genetic, degenerative disorders of the spinal cord characterized by progressive weakness and stiffness of the legs; Huntington's disease (HD) a hereditary progressive neurodegenerative disorder characterized by the development of emotional, behavioral, and psychiatric abnormalities and movement abnormalities; multiple system atrophy (MSA) a neurodegenerative disease marked by a combination of symptoms affecting movement, blood pressure, and other body functions; pathologic myoclonus; progressive supranuclear palsy; restless legs syndrome; Rett syndrome; spasticity; Sydenham's chorea; Tourette syndrome; and Wilson disease."*

(emphasis added). However, this passage does not indicate that all of the disorders which are listed here, and in particular RLS, are considered to be dystonia within the meaning of the invention of D24 or that they can be treated by the method according the invention of D24.

It can be summarized that D24 does not disclose that KW-6002 can be used to treat RLS. Consequently the subject matter of claim 1 of the patent-at-issue is novel.

6. Inventive step

6.1 Inventive step objections raised by Opponent I

Opponent I presented several lines of argument in view of inventive step.

6.1.1 Inventive step objection based on a combination of D5 with D6/D7/D8/D22

In point 4.1 of their Notice of Opposition Opponent I argued that a skilled person would have come to the subject matter of the patent-at-issue based on a combination of D5 with D6/D7/D8/D22. In essence Opponent I argued that D5 discloses that in general the medications that treat Parkinson's disease also provide effective treatment for RLS. Opponent I then turned to D6/D7/D8/D22 which teach that adenosine A_{2A} receptor antagonists can be used to treat Parkinson's disease and then concluded that a skilled person would use them against RLS. Opponent I then pointed out that RLS and PLMS (nocturnal myoclonus) are related so that a skilled person would make the same conclusion for nocturnal myoclonus. This line of argument is based on a misrepresentation of D5.

D5 is a review article which was published shortly before the priority date of the patent-at-issue and gives an overview over the clinical and pathophysiologic features of RLS. When discussing this reference Opponent I recited the passage on page 137, right column, first full paragraph. However, instead of reciting the full text of the passage he purposively distorted its sense by only giving part of the text. The full passage reads:

> ***"Brain Dopaminergic Function in RLS***
>
> *The serendipitous finding that levodopa at low doses provides almost complete relief from RLS (Akpinar, 1982; Montplaisir et al., 1986) provides the basis for the current, widely held view that RLS involves dopaminergic dysfunction. Moreover, in general the medications that treat Parkinson's disease also proved effective treatment for RLS. Centrally active dopaminergic antagonists have been reported clinically to exacerbate this condition whereas peripherally active dopaminergic antagonist does not (Wetter et al., 1999). Thus it seems reasonable to hypothesize that RLS involves a disruption of the dopaminergic function in the central nervous system, presumably (as noted earlier) at the subcortical levels of the brain."*

The subsequent passages also describe the connection between RLS and the dopaminergic system. Consequently a skilled person reading D5 would not have assumed that any type of Parkinson medication can be used for treating RLS but only that those types of Parkinson medications which are based on the dopaminergic system can be employed. This interpretation of D5 is in line with the teaching of the complete document which repeatedly

relates RLS to abnormal dopaminergic function and sets out that dopaminergic medications are the usual treatment of first choice for RLS and that their

"doses are low relative to those used for treatment of Parkinson's disease."

(D5: page 142, second column, last paragraph and page 143, second paragraph, lines 42 to 44).

Consequently a skilled person reading D5 would only have considered that dopaminergic medications which are suitable for treating Parkinson's disease can be used for treating RLS. Therefore, he would not have turned to any of D6/D7/D8/D22 which mention adenosine A_{2A} receptor antagonists. As was well-known in the art the

"mode of action [of adenosine A_{2A} receptor antagonists] is intrinsically different from that of the dopamine-related modulators used in most Parkinsonian therapies"

(D6: page 339, Box 1, first column, lines 20 to 26; emphasis added) or as is explained on page 94, right column lines 28 to 31 of D7:

"adenosine A_{2A} receptor antagonist [KW-6002] exerts the efficacy completely through the different target molecule and mechanism of action from dopaminomimetic drugs such as L-dopa."

(emphasis added). Because adenosine A_{2A} receptor antagonists act via a different mechanism than dopaminergic medications, a skilled person starting from D5 would not have considered them to be suitable to treat RLS. For the sake of completeness it is pointed out that KW-6002 does not have an affinity for dopamine receptors (D7: page 93, column 2, first paragraph under the heading "Discussion"; D13: page 1448, Chapter entitled "1.1. Biochemical Properties"). Therefore, a skilled person would not have considered it to be a dopaminergic medication and thus would not have been motivated to use it for the treatment of RLS or nocturnal myoclonus based on D5 for this further reason.

D5 is a thorough review on the clinical and pathophysiologic features of RLS which was published shortly before the instant priority date. It is interesting to note that it fails to indicate that any adenosine A_{2A} receptor antagonists might be suitable in treating RLS or

nocturnal myoclonus although according to Opponent I's opinion these therapeutic applications were so obvious.

6.1.2 Inventive step objection based on D12

In point 4.2 of the Notice of Opposition Opponent I tried to argue that a skilled person would have tried an adenosine A_{2A} receptor antagonist for treating RLS because allegedly there is a known equivalence between dopamine agonism and adenosine A_{2A} receptor antagonism, notably for the treatment of Parkinson's disease. Based on the argument that adenosine A_{2A} receptor antagonists can be used instead of dopamine agonists in the treatment of Parkinson's disease, Opponent I alleged that a skilled person would assume that this would be possible for other diseases such as RLS and nocturnal myoclonus. This position is based on an impermissible *ex post facto* analysis and not on an objective assessment of the prior art.

RLS and Parkinson's disease are distinct disorders with different etiologies. Although it may be true that dopaminergic agents can be used to treat both disorders this does not imply that a different class of compounds, namely adenosine A_{2A} receptor antagonists, which act through a completely different target molecule and mechanism of action (D6: page 339, Box 1, first column, lines 20 to 26; D7: page 94, right column lines 28 to 31), would do the same. Rather a skilled person would have no expectation that this would be possible.

D26 S. Aoyama et al., J. Neuroscience, 20(15), 5848–5852

discusses the interaction between adenosine A_{2A} receptors and dopamine D_2 receptors and explains that this interaction is not essential for the anti-Parkinson activity of adenosine A_{2A} receptor antagonists. In the abstract it is stated that

> *"blockade of A2AR rescues the behavioral parameters altered in D2R-/- mice. [...] These results show that A2AR and D2R have antagonistic and independent activities in controlling neuronal and motor functions in the basal ganglia. They also provide evidence that selective A2AR antagonists can exhibit their anti-parkinsonian activities through a nondopaminergic mechanism."*

It is concluded that

> *"Importantly, [adenosine] KW6002 restores the movement impairment in mutant mice in the absence of D2 receptors, indicating that its activity is independent of D2-mediated mechanisms. [...]*
>
> *In conclusion, our study shows that KW-6002 treatment of D2R-/- mice reestablishes their altered striatal gene expression and locomotor behavior. Blockade of A2ARs might decrease the neuronal activity of the striatopallidal indirect pathway in the absence of D2R-mediated signalling."*

(D26: page 5851, second column last two paragraphs). In addition, it is mentioned in D12 (page 68, first column, lines 1 to 3):

> *"that adenosine and dopamine exert opposing effects on the activity of the D_2-containing striatopallidal neurons"*

which relate to Parkinson's disease. However, no such an effect is known on the neurons which relate to RLS and there is no report on the effects of adenosine A_{2A} receptors on RLS.

As further evidence

> **D27** C. W. Schindler et al., Pharmacology, Biochemistry and Behavior 72 (2002) 857–863

is submitted. This document reports that the dopamine D2 agonist quinpirole showed the effect of decreasing locomotor activity on Sprague-Dawley rats (D27: abstract). On the other hand, adenosine A_{2A} receptor antagonists are known to increase the locomotor activity (D12: Table 2). Consequently a skilled person would not have been motivated to replace a dopamine agonist by an adenosine A_{2A} receptor antagonist in the treatment of RLS or PLMS.

6.1.3 Inventive step objection based on the scope of granted claim 1

In point 4.3 Opponent I argued that the scope of granted claims 1 and 2 was too broad. This objection is not applicable to the present claims.

6.1.4 Inventive step objection based on a combination of D10/D11/D19 with D6/D7/D8/D22

Opponent I argued in point 4.4 of his Notice of Opposition that if a skilled person used an adenosine A_{2A} receptor antagonist to treat Parkinson patients he would inevitably observe improvements of RLS and nocturnal myoclonus symptoms because these are frequent sleep dysfunctions in Parkinson patients.

This line of argument is contrary to the established case law of the Boards of Appeal at the EPO. Parkinson's disease and RLS/nocturnal myoclonus are distinct disorders. As long as the prior art does not explicitly disclose that RLS/nocturnal myoclonus is to be treated or is improved by the administration of an adenosine A_{2A} receptor antagonist, this teaching has not been made available to the public and both novelty and inventive step should be acknowledged (decision of the Enlarged Board of Appeal G2/88). Consequently the arguments presented by Opponent I are not conclusive.

6.1.5 Inventive step objection based on the contents of the US proceedings

In point 4.5 of the Notice of Opposition Opponent I tried to introduce the contents of the parallel US proceedings into the EP proceedings. As we had previously explained, the USPTO assesses both novelty and inventive step in a very different manner than the EPO, so that even if the examiner at the USPTO were to finally refuse the corresponding US application (which she has not) this would still not be indicative of the outcome of the opposition proceedings before the EPO. This is especially true because the claims which were discussed in the US office action are much broader than the claims currently pending in Europe. For the sake of completeness

D28 response to the US office action and a declaration prepared by Dr. Tomoyuki Kanda

are introduced into the proceedings. The arguments presented in the response as well as the statements in the declaration reinforce our position that the subject matter of the patent-at-issue is inventive. As Dr. Kanda explains in point 10 of the declaration there is no link or causality between RLS and Parkinson's disease. Specifically Parkinson's disease does not increase the risk for RLS and RLS does not increase the risk for Parkinson's disease. These findings indicate that RLS and Parkinson's disease do not share the same pathophysiological mechanism (point 11). Although RLS and Parkinson's disease have dopaminergic dysfunction in the central nervous system, dopaminergic medications treat RLS only as centrally acting dopaminergic agents not as anti-Parkinson agents. Therefore, a skilled person who understands the physiopathology of RLS would not have been motivated to administer a medication which is suitable for treating Parkinson's disease to a patient suffering from RLS unless it is also a central acting dopaminergic agent. KW-6002, which is required by the instant claims, is not a centrally acting dopaminergic agent (D7: page 93, column 2, first paragraph under the heading "Discussion"; D13: page 1448, Chapter entitled "1.1. Biochemical Properties") but rather an adenosine A_{2A} receptor antagonist.

The present inventors have found that KW-6002 or a pharmaceutically acceptable salt can be used to treat RLS or nocturnal myoclonus. This finding is especially surprising because KW-6002 is known to be an adenosine A_{2A} receptor antagonist.

As is explained in D12 and is summarized in Table 2 on page 72 of this reference, adenosine A_{2A} receptor antagonists are known to increase locomotion activity. Therefore, they are proposed as a therapeutic for Parkinson's disease. In contrast thereto, adenosine A_{2A} receptor agonists are known to decrease locomotion activity and to increase slow wave and paradoxical sleep. For this reason it is proposed to employ them in the treatment of sleep disorders. The increase in locomotion activity is specifically shown for KW-6002 in D7 (title), D13 (page 1448, second column, section 1.2.), and D22 (col. 44, Experimental Example 3). Based on the understanding that adenosine A_{2A} receptor antagonists increase locomotion activity whereas adenosine A_{2A} receptor agonists decrease locomotion activity and improve sleep it was counter-intuitive to chose adenosine A_{2A} receptor antagonists to treat the motor disorders RLS and nocturnal myoclonus, which are characterized by increased activity of the patients and impaired sleep. For these additional reasons inventive step should be acknowledged.

6.2 Inventive step objections raised by Opponent II

Opponent II argued that claim 2 of the patent-at-issue lacks inventive step in view of D24. He based this line of argument on the allegation that the priority claim of the patent-at-issue is invalid.

As we have shown in point 3 above, the priority claim of the patent-at-issue with respect to claim 2 is valid. Therefore, D24 is prior art according to Art. 54(3) EPC and can not be taken into account when inventive step is assessed.

Solely as a precautionary measure in case the opposition division should not follow our argument, the following comments on inventive step in view of D24 are given.

Claim 2 of the patent-at-issue relates to the use of KW-6002 for the treatment of nocturnal myoclonus.

In the section which describes the invention of D24 it is mentioned that

> *"The invention also includes methods of treating movement disorders comprising administering an effective amount of at least one adenosine A_{2A} receptor antagonist to a patient in need thereof. Such treatment can be therapeutic such as to treat tremors, bradykinesias, gait, dystonias, or tardive dyskinesias or other extrapyramidal syndromes, or preventative such as to prevent or lessen the effects of drugs that cause movement disorders."*

(D24: page 45, lines 7 to 12). This section, which describes which disorders can be treated, does not mention that the adenosine A_{2A} receptor antagonist can be used to treat nocturnal myoclonus. The only references to "myoclonus" which can be found in D24 are in the section which refers to the prior art (D24: page 1, line 15; page 5, line 2 and page 7, line 28). For example on page 7, lines 28 and 29 of D24 it is mentioned that various diseases involving dystonias are known:

> *"Diseases involving dystonias include hereditary spastic paraplegia (HSP), a group of genetic, degenerative disorders of the spinal cord characterized by progressive weakness and stiffness of the legs; Huntington's disease (HD) a hereditary progressive neurodegenerative disorder characterized by the*

development of emotional, behavioral, and psychiatric abnormalities and movement abnormalities; multiple system atrophy (MSA) a neurodegenerative disease marked by a combination of symptoms affecting movement, blood pressure, and other body functions; pathologic myoclonus; progressive supranuclear palsy; restless legs syndrome; Rett syndrome; spasticity; Sydenham's chorea; Tourette syndrome; and Wilson disease."

However, this passage does not teach or suggest that all of the various types of dystonias which are listed here, and in particular myoclonus, are considered to be dystonia within the meaning of the invention of D24 or that they can be treated by adenosine A_{2A} receptor antagonists.

Opponent II argued that since nocturnal myoclonus merely refers to myoclonus that occurs during sleep, it would have been obvious to those of ordinary skill in the art that any adenosine A_{2A} receptor antagonist that is disclosed in D24 and which is effective in the treatment of myoclonus in general would be useful in the treatment of nocturnal myoclonus in particular. This assessment is based on an oversimplification and on hindsight.

As can be seen from the enclosed copy of

D29 Internet printout from Merck.com "Myoclonus"

the general term "myoclonus" is not a diagnosis of a disease but rather a symptom. Myoclonus merely means that brief, involuntary twitching of a muscle or a group of muscles occurs. Therefore, "pathological myoclonus" is pathological twitching of muscles. As is explained in D29, myoclonus can have a wide variety of causes and can thus require a wide variety of treatments based on the underlying disorder.

In contrast thereto, nocturnal myoclonus is a defined movement disorder with a specific (albeit unknown) etiology. Consequently a skilled person reading the statement that "pathological myoclonus" is a disease involving dystonia would not automatically assume that any type of pathological myoclonus and in particular nocturnal myoclonus can be treated by the same medication.

Rather the statement on page 45, lines 7 to 12 of D24 according to which "dystonia" can be treated with adenosine A_{2A} receptor antagonists has to be seen in the context of the description of the invention of this reference. In Example 1 of D24 Parkinson patients were treated with a combination of L-DOPA and KW-6002 (invention) or L-DOPA alone (comparative). It was surprisingly shown that the patients which received KW-6002 had reduced "early morning dystonia", i.e., early morning twitching. This twitching has nothing to do with nocturnal myoclonus but is rather a sign that the effects of the last dose of medication which was administered before going to bed are wearing off or that the Parkinson disease itself was effectively treated by KW-6002. Consequently a skilled person reading D24 as a whole would not deduce that nocturnal myoclonus can be treated by the adenosine A_{2A} receptor antagonists disclosed therein.

Furthermore, as was explained in point 6.1.5 above, it was actually counter-intuitive to chose adenosine A_{2A} receptor antagonists to treat the motor disorder nocturnal myoclonus, which is characterized by increased activity of the patients and impaired sleep.

For these reasons D24 does not render the subject matter of the patent-at-issue obvious.

7. Summary

It can be summarized that the new main request fulfils the requirements of the EPC. Therefore the request to maintain the patent in an amended form is fully justified.

Natalia Berryman

Dr. Natalia Berryman
European Patent Attorney

Encl.:
Main request
D26 S. Aoyama et al., J. Neuroscience, 20(15), 5848–5852
D27 C. W. Schindler et al., Pharmacology, Biochemistry and Behavior 72 (2002) 857–863
D28 Response to the US office action and a declaration prepared by Dr. Tomoyuki Kanda
D29 Internet printout from Merck.com "Myoclonus"